Advances in nutritional modifications of infant formulas[1–4]

Jane D Carver

ABSTRACT

Modifications to infant formulas are continually being made as the components of human milk are characterized and as the nutrient needs of diverse groups of infants are identified. Formulas with long-chain polyunsaturated fatty acids added in amounts similar to those in human milk have recently become available in the United States; infants fed these formulas or human milk have higher tissue concentrations of long-chain polyunsaturated fatty acids and reportedly have better visual acuity than do infants fed nonsupplemented formulas. Selenium, an important antioxidant, is present in higher concentrations in human milk than in nonfortified cow milk–based formula, and the selenium intakes of infants fed nonfortified formulas are reported to be at or below recommended levels. Blood selenium concentrations and plasma glutathione peroxidase activity are higher in infants fed selenium-supplemented formulas or human milk than in infants fed nonfortified formulas. Nucleotides and their related products play key roles in many biological processes. Although nucleotides can be synthesized endogenously, they are considered "conditionally essential." Nucleotide concentrations in human milk are higher than in unsupplemented cow milk–based formulas, and studies in animals and human infants suggest that dietary nucleotides play a role in the development of the gastrointestinal and immune systems. Formulas for preterm infants after hospital discharge are designed to meet the needs of a population in whom growth failure is common. Several studies have shown that preterm infants fed nutrient-enriched formulas after hospital discharge have higher rates of catch-up growth than do infants fed standard term-infant formulas. *Am J Clin Nutr* 2003;77(suppl):1550S–4S.

KEY WORDS Long-chain polyunsaturated fatty acids, selenium, nucleotides, preterm infants, nutrition

INTRODUCTION

Remarkable improvements have been made to infant formulas over the past 50 y. In the mid-20th century, formula-fed infants were usually given cow milk–based infant formulas or homemade formulations of evaporated milk, sugar, and water. Today, options include soy formulas, lactose-free formulas, formulas with added fiber or rice starch, protein hydrolysates, preterm infant formulas, and formulas for infants with special conditions such as metabolic disorders. New formulas continue to be developed, and existing formulas undergo frequent modifications as more components of human milk are characterized and their physiologic functions are determined. Human milk contains hormones, immune factors, growth factors, enzymes, and viable cells, most of which cannot practically be added to infant formulas. Furthermore, the complex interactions of these bioactive substances should be understood before they are added to formula. Modifications that have resulted in formulas with compositions and functions closer to those of human milk include the addition of long-chain polyunsaturated fatty acids (LCPs) and nucleotides and the enrichment of formula with selenium (**Table 1**). The introduction of nutrient-enriched formulas for preterm infants after hospital discharge is an example of a new type of formula designed to meet the needs of infants with special nutrient requirements.

LONG-CHAIN POLYUNSATURATED FATTY ACIDS

The predominant 20–22-carbon LCPs in human milk are arachidonic acid (AA; 20:4n−6) and docosahexaenoic acid (DHA; 22:6n−3). Until recently, infant formulas contained only the 18-carbon precursors to AA and DHA, namely the essential fatty acids linoleic acid (18:2n−6) and α-linolenic acid (18:3n−3), respectively. Formulas with AA and DHA added in amounts patterned after those in human milk are now commercially available. The milk of women from populations who consume large quantities of fish, such as the population of Japan, may contain >1% of fatty acids as DHA, whereas milk from populations who consume lesser amounts, such as the population of the United States, may contain only 0.1–0.2%. The AA content of human milk is less variable and less dependent on maternal dietary intake. AA concentrations are similar across divergent populations and range from ≈0.4–0.6% of total fatty acids (1–3). LCP-supplemented formulas generally contain ≈0.3–0.6% AA and 0.2–0.4% DHA. Sources include microalgal and fungal oils, egg yolk–derived lipids, and marine oils (4).

LCPs play diverse physiologic and metabolic roles. AA is the precursor to the "2" series of eicosanoids, which are important biomediators. LCPs are also structural components of membranes. The fatty acid composition of membranes can affect tissue function by modifying membrane fluidity, and it can influence signal transduction cascades by altering the balance of eicosanoids synthesized and by affecting gene transcription (5, 6).

[1] From the Department of Pediatrics, University of South Florida College of Medicine, Tampa.

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[4] Address reprint requests to JD Carver, Department of Pediatrics, University of South Florida College of Medicine, 17 Davis Boulevard, Suite 200, Tampa, FL 33606. E-mail: jcarver@hsc.usf.edu.

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TABLE 1
Summary of modifications made to infant formulas

Modification	Rationale	Observed outcome
Addition of 20–22-carbon long-chain polyunsaturated fatty acids	None in most unsupplemented formulas	Better visual acuity in preterm infants
Supplementation with selenium	Amounts in formula less than those in human milk	Higher blood concentrations of selenium and glutathione peroxidase
Supplementation with nucleotides	Amounts in formula less than those in human milk	Increases in measures of immune responsiveness
Formulas designed for preterm infants after hospital discharge	Growth deficits in infants fed term formulas	Higher rates of catch-up growth

AA and DHA are major components of cell membrane phospholipids and are the predominant LCPs of the central nervous system. LCPs accrue rapidly in the brain during the period of maximal brain growth, which lasts from the last trimester of pregnancy until ≈2 y of age in humans (6–8). Postnatally, infants obtain LCPs from the diet or by de novo synthesis. Although both term and preterm infants can synthesize AA and DHA from their 18-carbon precursors, factors such as prematurity and the ratios and amounts of precursors can affect the rate of synthesis (4). Infants fed formulas without added LCPs generally have lower blood LCP concentrations than do human milk–fed infants; this is especially true in infants born prematurely (4, 6, 8). Reports that term infants fed human milk have higher DHA concentrations in their cerebral tissues than do formula-fed infants led to speculation that the superior neurodevelopment of human milk–fed infants compared with that of formula-fed infants may be due, in part, to the higher dietary DHA intake of the milk-fed infants (9, 10). Because DHA is a major component of retinal photoreceptor membranes (4), reports of better visual acuity in human milk–fed infants than in formula-fed infants, particularly among infants whose mothers consumed high quantities of DHA (11), led to speculation that LCP-supplemented formula might enhance development of the visual system.

Over the past 10 y, >2 dozen studies have reported effects of LCP supplementation in infants. Most of the studies focused on effects on growth, cognitive development, and visual acuity. Most of the studies reported normal growth in infants fed the newer LCP formulas that contain both AA and DHA and little or no eicosapentaenoic acid (20:5n−3). Although studies of cognitive development do not show consistent effects, several studies of visual acuity show a benefit, particularly for infants born prematurely (1, 4, 6, 8). A meta-analysis and a systematic review of data from preterm (12) and term (13) infants, respectively, indicate advantages of DHA-supplemented formulas over unsupplemented formulas in both behaviorally based and electrophysiologically based measurements of visual acuity. The different results may be due, in part, to the different concentrations, ratios, and sources of LCPs used; to insufficient numbers of infants studied; and to different study designs. The long-term effects of feeding LCP-supplemented formula remain to be determined.

Relatively little attention has been paid to the effects of dietary LCPs on the immune system. Studies in animals showed significant effects of dietary LCPs on immune function, which are probably due to their role as eicosanoid precursors (14). Field et al (15) reported that infants fed LCP-supplemented formula had lymphocyte populations and values for cytokine production and antigen maturity that were more similar to those of human milk–fed infants than to those of infants who received unsupplemented formula.

SELENIUM

Selenium is an essential micronutrient that functions mainly in association with proteins or as a constituent of them; 11 selenoproteins have been identified to date (4, 16). Selenium is best known for its role as an antioxidant. It is a component of the glutathione peroxidase group of enzymes that remove toxic peroxides and protect cell membranes from oxidative damage. Epidemiologic studies have identified selenium as a protective factor against oxidative stress in relation to heart disease and drug metabolism, and selenium is postulated to be a dietary factor that plays a role in cancer prevention. Although overt selenium deficiency is relatively rare, prolonged, inadequate intakes can impair biochemical functions and thus predispose persons to illnesses that are associated with metabolic stress but do not involve the development of overt disease (4, 16). Severe selenium deficiency in infants is associated with skeletal and cardiac myopathy and is generally associated with long-term hyperalimentation that contains little or no selenium (4, 16).

Selenium concentrations in human milk range from 15 to 20 μg/L depending on geographic location; concentrations are lower in the milk of women from geographic locations, including New Zealand and parts of China, that have low soil selenium concentrations. Selenium concentrations in unsupplemented cow milk–based infant formulas range from 2 to 13 μg/L and are dependent on the selenium intake of dairy cows. The selenium intakes of infants fed formulas without supplemental selenium are reported to be near or below recommended intakes (4, 17).

Selenium status is assessed by measuring total dietary intake, plasma or serum selenium concentrations, erythrocyte selenium concentrations, plasma and erythrocyte glutathione peroxidase concentrations, and urinary excretion. Plasma or serum selenium concentrations indicate short-term selenium status, whereas glutathione peroxidase concentrations indicate longer-term status. Blood selenium concentrations generally increase from birth to 6 mo of age in breastfed infants; however, in infants fed unsupplemented formulas, the concentrations remain stable or decrease for several months after birth (18–20). The postnatal decrease may be due to intakes that are inadequate to meet the needs of the rapidly growing infant (4, 18–20). Several studies showed that plasma and serum selenium concentrations and plasma glutathione peroxidase activity are higher in infants fed human milk or formula supplemented with selenium than in infants fed formulas that do not contain supplemental selenium (18–21).

Selenium supplementation of formulas may be particularly important for preterm infants because they experience rapid postnatal growth and have less fetal accretion, lower plasma concentrations of selenium and glutathione peroxidase at birth, and a higher risk of exposure to oxidative stress than do term infants (4, 22). It has been suggested that poor selenium status is a risk factor for the development of chronic lung disease. Plasma selenium concentrations decrease at a more rapid rate in preterm infants who develop chronic lung disease than in those who do not, and the decreasing concentrations are associated with higher respiratory morbidity (4). Several investigators have reported higher plasma concentrations of selenium and glutathione peroxidase in preterm infants fed selenium-supplemented formula than in infants fed unsupplemented formula (4, 22, 23).

NUCLEOTIDES

The terms "semiessential" or "conditionally essential" have been used to describe the role of nucleotides in human nutrition. These nutrients may become essential when the endogenous supply is insufficient for normal function, even when their absence from the diet does not lead to a classic clinical deficiency syndrome. Conditions under which these nutrients may become essential include certain disease states, periods of limited nutrient intake or rapid growth, and the presence of regulatory or developmental factors that interfere with the full expression of endogenous synthetic capacity. Under these conditions, dietary intake of nutrients spares the organism the cost of de novo synthesis or salvage and may optimize tissue function (24, 25).

Nucleotides and their related metabolic products play key roles in many biological processes. They serve as nucleic acid precursors, physiologic mediators, constituents of coenzymes, and sources of cellular energy. De novo nucleotide synthesis is metabolically costly, and nucleotides can be obtained more efficiently from the diet or through the nucleotide salvage pathway. Although most dietary nucleotides are catabolized and excreted, up to 5% are incorporated into tissues, particularly during periods of rapid growth and limited food intake (24, 25).

Nucleotides are abundant in the diets of adults and weaned infants. However, concentrations of nucleotides in unsupplemented cow milk–based formulas are lower than those in human milk. A wide range of nucleotide concentrations, from 30 to >70 mg/L, has been reported in human milk. Nucleotide-supplemented formulas generally contain between 20 and 70 mg/L (25, 26).

Data suggest that dietary nucleotides play a role in the growth and differentiation of the gastrointestinal tract. The intestinal tissues of animals fed nucleotide-supplemented diets have more mucosal protein and DNA, higher villus height and disaccharidase activities, and better recovery after intestinal injury than do those of animals fed nucleotide-free diets (24, 25, 27). LeLeiko et al (28) reported that dietary nucleotides affect the gene expression of gastrointestinal enzymes. Two studies in infants indicate that dietary nucleotides may protect against diarrheal disease (29, 30), and a recent study reported that dietary nucleotides may affect blood flow velocities in the mesenteric arteries of infants after a meal (31).

Dietary nucleotides also affect the immune system. Compared with feeding nucleotide-free diets, feeding nucleotide-supplemented diets has been associated with higher values for the following immune responses in animals: graph versus host disease mortality, rejection of allogeneic grafts, delayed cutaneous hypersensitivity, alloantigen- and mitogen-induced lymphoproliferation, natural killer cell activity, macrophage activation and phagocytic capacity, resistance to microbial challenge, and spleen and lymph node production of cytokines (25). Although the mechanisms remain unclear, Nagafuchi et al (32) speculate that dietary nucleotides up-regulate the immune response of type 1 T helper cells in systemic immunity. Several studies in infants also indicate an effect of dietary nucleotides on the immune system. Infants fed nucleotide-supplemented formula had higher serum concentrations of antibodies to *Haemophilus influenzae* type b and diphtheria after immunization than did infants fed standard formula (30). Other investigators reported greater natural killer cell activity (33) and higher concentrations of immunglobulin G antibody to β-lactoglobulin in infants fed nucleotide-supplemented formula than in those fed standard formula (34). Although most studies of dietary nucleotides did not report effects on somatic growth, Cosgrove et al (35) found that small-for-gestational-age term infants who were fed formula supplemented with nucleotides had higher growth rates to 6 mo of age than did those who were fed unsupplemented formula.

FORMULAS FOR PRETERM INFANTS AFTER HOSPITAL DISCHARGE

As the rate of survival of preterm infants increases, their nutritional needs after hospital discharge are becoming an increasingly important issue. Many preterm infants are discharged from the hospital with significant growth restriction and morbidities that can affect nutrient intake and growth. The National Institute for Child Health and Development Neonatal Research Network reported that from 1991 to 1996, increases in survival were particularly apparent for infants weighing < 1000 g at birth (36). Growth failure, defined as a weight below the 10th percentile at 36 wk postmenstrual age, was present in 99% of these infants.

The American Academy of Pediatrics recommends that preterm infants be fed sufficient amounts of all nutrients to achieve postnatal rates of growth and nutrient accretion that approximate those of a normal fetus during the same period (37). However, this goal is rarely met because of factors such as metabolic instability, gastrointestinal immaturity, clinical setbacks, and withholding of feedings because of intolerance, operations, or procedures (36, 38). Embleton et al (39) reported that by the end of the fifth week of life, infants born at ≤ 30 wk of gestation had cumulative energy and protein deficits of 813 ± 542 kcal/kg and 23 ± 12 g/kg, respectively, and z scores for weight of −1.14 ± 0.6. Other investigators also reported low body stores of nutrients and deficient bone mineralization in preterm infants at hospital discharge (38, 40, 41).

Most preterm infants experience significant catch-up growth after hospital discharge. However, their mean gestation-corrected growth measurements during infancy and childhood are lower than those of infants born at term (42, 43). The significance of catch-up growth for long-term development is unclear. However, poor somatic growth during the first year of life is associated with delays in the neurodevelopment of preterm infants (44, 45). Small head-circumference measurements, in particular, may have long-term prognostic significance for very-low-birth-weight infants. Hack et al (46) reported that subnormal head size at 8 mo of age predicted the Bayley Mental Development Index score at 20 mo of age, and Gross et al (47) reported that infants with the greatest

growth in head circumference in the first 6 wk of life had better neurodevelopment to 15 mo of age than did those with less growth in head circumference. Hack et al (48) have suggested that the first year of life provides an important opportunity for human somatic and brain growth to compensate for earlier deprivation.

Although the role of nutrition in improving developmental outcomes is unclear, accumulating data suggest that feeding nutrient-enriched formulas after hospital discharge can increase the rate of catch-up growth. Several investigators reported that preterm infants fed nutrient-enriched formulas after hospital discharge had significantly greater increases in weight (49–51), length (49–52), head circumference (50–52), and bone mineralization (40, 41, 50) than did those fed standard term-infant formulas. In several of those studies, volume intakes were lower among the infants fed the enriched formulas (50–52), indicating some ability of infants to self-regulate intakes on the basis of nutrient density. However, despite the lower volume intakes, protein and energy intakes were higher. The most significant growth-enhancing effects of the enriched feedings were generally seen within the first few months after discharge and were most evident among male infants and infants with the lowest birth weights. The effects of nutrient-enriched feedings on neurodevelopment were not measured, or there were no effects reported. Areas for additional study include the effects of nutrient-enriched formulas on the neurodevelopment of infants with conditions that may negatively affect rates of catch-up growth, such as chronic disease, in utero growth retardation, and extremely low birth weight.

CONCLUSION

In summary, changes continue to be made to infant formulas, and these changes generally result in products with compositions and functions closer to those of human milk. In addition, new formulas are being developed to meet the needs of infants with special nutrient needs. Formulas with LCPs added in amounts similar to those in human milk are now available in the United States, and data suggest that they may benefit the development of the visual system. Fortification of formula with selenium results in higher blood selenium concentrations and is associated with higher glutathione peroxidase activity. Several studies suggest that nucleotides in formula enhance the development of the immune and gastrointestinal systems. Formulas for preterm infants after hospital discharge are designed to meet the needs of a population at risk of developing growth and nutrient deficiencies, and several studies reported that catch-up growth was greater in infants fed these new formulas than in those fed standard term-infant formulas. Through ongoing studies, researchers will continue to characterize the complex components of human milk and the specific nutrient needs of diverse groups of infants. Long-term studies with large groups of infants are needed to determine whether the biochemical effects associated with modifications to infant formulas are associated with functional outcomes.

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